Here Comes the Sun: Recognition of UV-Damaged DNA

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The first step in the repair of DNA damage is lesion detection. In this issue, Scrima et al. (2008) report the structure of the complex of DNA Damage-Binding Protein 1 (DDB1) and DDB2 bound to a DNA photodimer, providing critical insight into the repair of DNA damage caused by ultraviolet light.

Excessive exposure to ultraviolet (UV) radiation from the sun leads to skin cancer. Yet, insufficient exposure leads to vitamin D deficiency. Humans have evolved two adaptations for dealing with the yin/yang of sun exposure: skin pigmentation and nucleotide excision repair. Increased melanin pigmentation in dark skin protects populations dwelling at equatorial latitudes from skin cancer, whereas decreased pigmentation in fair skin maximizes vitamin D activation in populations at polar latitudes. However, fair skin would be an untenable phenotype were it not for nucleotide excision repair, which removes UV-induced DNA lesions. For example, the loss of nucleotide excision repair in the autosomal recessive disease xeroderma pigmentosum leads to sun hypersensitivity and skin cancer. In this issue, Scrima et al. (2008) show how a complex of DNA Damage-Binding Protein 1 (DDB1) and DDB2 recognizes photolesions in DNA to marshal the nucleotide excision repair machinery.

Nucleotide excision repair recognizes and removes UV-induced lesions in a background of billions of normal base pairs and accomplishes this daunting task by two different mechanisms: transcription-coupled repair and global genomic repair. Transcription-coupled repair recognizes lesions on transcribed DNA by the stalling of RNA polymerase II at the site of damage (Figure 1A). Global genomic repair targets damage throughout the genome by the coordinated action of two heterodimeric proteins, DDB1-DDB2 and XPC-HR23. Mutations in DDB2 and XPC are implicated in xeroderma pigmentosum complementation groups E and C, respectively.

Initially, the DDB1-DDB2 complex binds to the lesion and then recruits XPC-HR23. DDB1 and CULLIN 4 then form an E3-ubiquitin ligase complex, which ubiquitinates DDB2, XPC, and histone proteins (Sugasawa et al., 2005). Ubiquitination of DDB2 and XPC may mediate the hand-off of the lesion site from DDB1-DDB2 to XPC-HR23. Histone ubiquitination may allow the nucleotide excision repair proteins to access nucleosomal DNA.

A longstanding question has been how DDB1-DDB2 recognizes the broad range of lesions targeted by nucleotide excision repair (Tang and Chu, 2002). In vitro, DDB1-DDB2 binds with high affinity to 6-4 photoproducts, which generate marked distortion of the DNA double helix, and it binds with lower affinity to cyclobutane pyrimidine dimers (CPD), which produce only moderate helical distortion. In addition, DDB1-DDB2 binds to DNA with crosslinked bases (due to cisplatin, nitrogen mustard, or psoralen treatment) but also binds to DNA with abasic sites, the antithesis of crosslinked bases.

Scrima et al. now report the crystal structures of the DDB1-DDB2 complex bound to two different DNA lesions, a bulky 6-4 photoproduct and an abasic analog. In both cases, the DNA is unwound and bent, and two nucleotides (the 6-4 photoproduct or the abasic site with its 3′ neighbor) are flipped out of the double helix (Figure 1B). While DDB1 stabilizes DDB2 but does not contact DNA, DDB2 interacts extensively with the distorted DNA backbone and the widened minor groove adjacent to the lesion. DDB2 contains a shallow binding pocket for the flipped out nucleotides, but the interactions are limited, leaving the damaged nucleotides largely exposed to solvent.

Structural, biochemical, and molecular dynamics studies suggest a general mechanism in which DNA repair proteins recognize lesions by detecting increased flexibility in the DNA due to destabilized base stacking (Yang, 2008). Protein binding would then mold the damaged DNA into a defined structure that complements the recognition protein. For example, when complexed with T4 endonuclease V, photolyase, or Rad4, the CPD-containing DNAs are kinked and unwound, and either the crosslinked nucleotides or their base-pairing partners are flipped out (Mees et al., 2004; Min and Pavletich, 2007; Vassylyev et al., 1995). Thus, lesion recognition could be based on a reduction in DNA rigidity induced by a lesion rather than a specific interaction with the damaged bases (Yang, 2008). The same mechanism now appears to occur for DDB1-DDB2 bound to either a 6-4 photoproduct or an abasic site. Recognition based on distortion explains how DDB1-DDB2 can target a broad range of lesions for nucleotide excision repair.

Nucleosomes may enhance damage-induced distortion by bending the DNA around the histone core. Scrima et al.

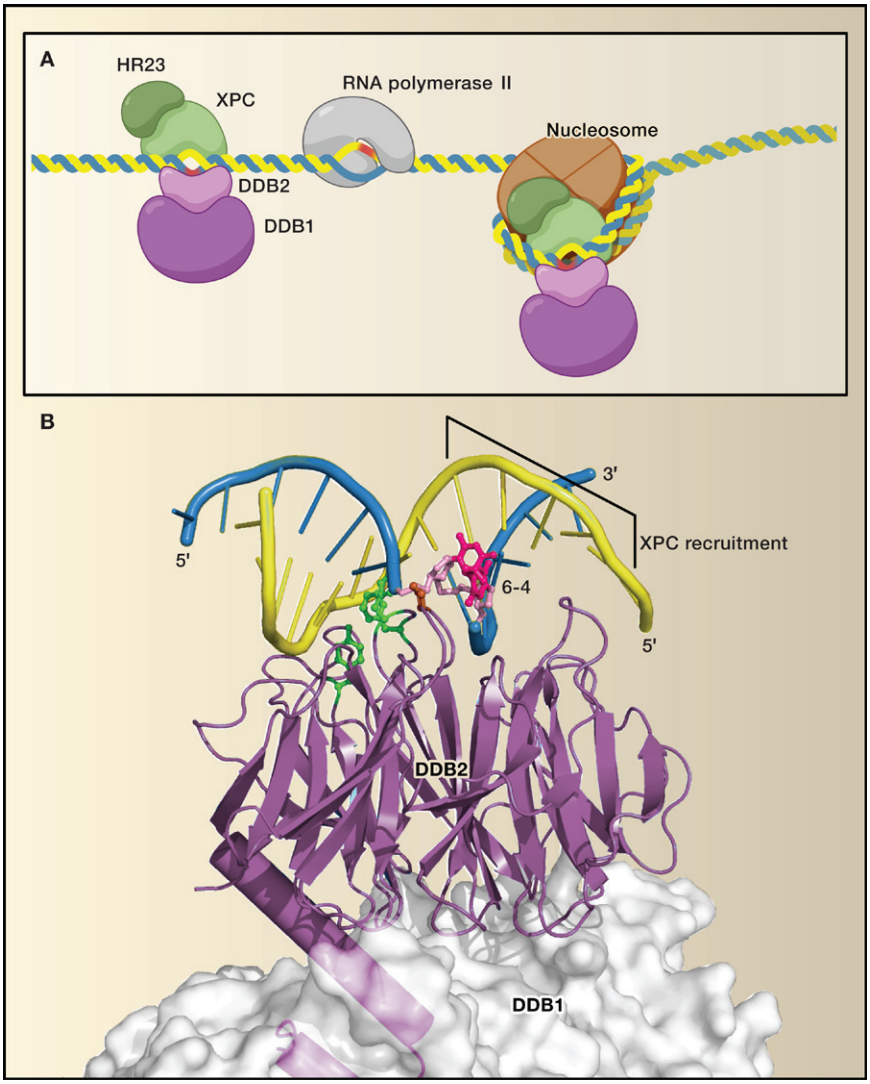

Figure 1. Recognition of Damaged DNA for Nucleotide Excision Repair

(A) Two pathways for damage recognition. Transcription-coupled repair recognizes lesions (red) when RNA polymerase II stalls at a damaged base on the transcribed DNA strand. Global genomic repair recognizes lesions by binding of DDB1-DDB2 and then XPC-HR23, targeting lesions on transcribed and nontranscribed DNA strands as well as DNA sequestered in nucleosomes. Histone proteins are likely displaced upon XPC-HR23 binding.

(B) The crystal structure of DDB1-DDB2 complexed with a 6-4 photoproduct. DDB2 shown in a purple ribbon diagram is stabilized by DDB1 shown as a semitransparent molecular surface. F371, H373, and Y393 are inserted into the DNA minor groove (highlighted in green); P191, which distorts the damaged strand, is highlighted in brown. The undamaged DNA strand is shown in yellow, and the damaged strand in blue, with the 6-4 photoproduct shown in light pink (backbone) and dark pink (bases). The gray bracket indicates where XPC may be recruited to bind the undamaged DNA strand.

suggest that DDB1-DDB2 may recognize DNA lesions in nucleosomes and recruit XPC to the lesion (Scrima et al., 2008). Indeed, Rad4, the yeast homolog of XPC, does not bind to the lesion but to the undamaged DNA strand (Min and Pavletich, 2007). Strand separation occurs due to the lesions and may be enhanced in the presence of DDB1-DDB2.

After initial lesion recognition by DDB1-DDB2 and recruitment of XPC-HR23, the specificity of nucleotide excision repair may be enhanced in the subsequent excision steps. Neither DDB1-DDB2 (Scrima et al., 2008) nor the yeast XPC homolog Rad4 (Min and Pavletich, 2007) differentiate between substrates for nucleotide excision repair (such as UV-induced photoproducts) from abasic lesions, mismatched base pairs, or undamaged single-stranded DNA, which are not substrates for nucleotide excision repair. Other factors recruited by XPC-HR23 and ubiquitination may play a role in discriminating against DNA structures that are not subject to nucleotide excision repair.

The DDB1-DDB2 structure also provides a new mode of protein-DNA binding. It represents the first structure of a β propeller protein bound to DNA at a specific site. DNA-binding proteins predicted to have similar β propeller structures, such as the V(D)J recombination activating protein RAG2, can be modeled onto DNA based on the structure of the DDB1-DDB2 complex bound to DNA.

Despite their tight association, the DDB1 and DDB2 subunits have evolved independently. DDB1 homologs exist in mammals, fruit flies, nematodes, fission yeast, and the budding yeast *Saccharomyces cerevisiae* (Zaidi et al., 2008). In fact, DDB1 often associates with proteins other than DDB2. For example, DDB1 also forms an E3-ubiquitin ligase complex with CSA (Cockayne Syndrome complementation group A), which is required for transcription-coupled repair and is mutated in patients with Cockayne Syndrome (Fousteri et al., 2006).

By contrast, DDB2 homologs exist only in mammals (Tang and Chu, 2002). Thus, DDB2 represents a recent evolutionary adaptation. The structure of the DDB1-DDB2 complex demonstrates that DDB2 plays the role of UV damage recognition for global genomic repair. Interestingly, in humans but not in mice, p53 activates transcription of DDB2, enhancing damage recognition after cells are exposed to UV (Tan and Chu, 2002). Perhaps the evolution of DDB2 has played a role in human history by increasing the viability of fair skin, which may have helped humans colonize polar latitudes.

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